PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 122233/14AJC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/NZ2003/000115**	International Filing Date *(day/month/year)* 5 June 2003	Priority Date *(day/month/year)* 5 June 2002
International Patent Classification (IPC) or national classification and IPC Int. Cl. [7] A61K 9/22, 9/54, 39/00, 39/08, A61P 33/10, 31/04		
Applicant AGRESEARCH LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand December 2003	Date of completion of the report 11 August 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA e-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **TERRY SUMMERS** Telephone No. (02) 6283 3126

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ2003/000115

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-3, 5, 7-26** as originally filed,
pages , filed with the demand,
pages **4, 6**, received on **6 July 2004** with the letter of **6 July 2004**

☒ the claims, pages **29-30,** as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **27-28,** received on **6 July 2004** with the letter of **6 July 2004**
pages **31-32,** received on **9 August 2004** with the letter of **9 August 2004**

☒ the drawings, pages **1/4 -4/4** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-30**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-30**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-30**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

This report refers to the following documents cited in the International Search Report:

D1 WO 2000/074655 A2
D2 WO 2001/007079 A1
D3 US 6010492 A
D4 Gupta R K et al
D5 Cleland J L et al.
D6 Theeuwes F and Yum S I

The invention concerns a pulsatile single administration drug delivery system that allows for a single administration of an biologically active agent(s) to be released as at least three doses over a predetermined period of time. The invention is characterised by at least three progressively increased dosages of the biologically active agent(s). The pulsatile drug delivery system is particularly relevant to vaccination regimes as it avoids the need for repeated booster immunisations. Claim 1 defines a pulsatile drug delivery process. Claim 12 defines a pulsatile drug delivery composition.

D1 discloses a two pulse gastrointestinal delivery system comprising a swellable core containing an active agent surrounded by an degradable inner coat and an outer coat that surrounds the inner coat containing further active agent. The outer coat provides a first pulse and the core provides a delayed second pulse. Although the amount of active agent in the core and outer coat are the similar, Figures 22 and 24 show a higher release from the second pulse (ie release from the core).

D2 discloses a pulsatile single immunisation vaccine delivery system preferably for Clostridium. The citation discloses various delivery means for achieving the pulsed delivery such as encapsulation of the active in multiple or graduated layers of biodegradable substances; bolus type or syringe devices may be used - see for example Figures 1 and 2. D2 further discloses at page 10 lines 7-13 that the second pulse has a higher release the first pulse. This is clear from words "burst of higher release" at lines 7-8 when read in context with the entire paragraph.

D3 discloses a drug delivery device capable of delivering subsequent doses of a drug.

D4 discloses a pulsatile single immunisation vaccine delivery system comprising biodegradable PLGA microspheres. The citation discloses a pulsed tetanus toxoid vaccine comprising a low dose first pulse (immediate release TT $AlPO_4$,0.05Lf)) and a high dose second pulse (delayed release TT PLGA microspheres, 0.5Lf) (see abstract, page 70 last paragraph and Fig 2 •-•)

Supplemental Box I
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

D5discloses a pulsatile single immunisation vaccine delivery system comprising biodegradable PLGA microspheres for HIV. The immunisation regime comprises an immediate release first pulse (soluble rgp120) and a delayed release second pulse (rgp120 in biodegradable PLGA microspheres). The dose of the second pulse is greater than the first pulse (see paragraph bridging columns 1 and 2 of page 1490, particularly column 2 lines 4-7).

D6 discloses the ALZET osmotic pump described at page 8 of the present specification (see the abstract and figures).

The amended claims are novel and involve an inventive step when compared with D1- D6. These documents neither disclose nor suggest pulsatile single administration drug delivery systems of ***at least three*** progressively increasing doses of the biologically active agent(s).

It is an object of the present invention to address the foregoing problems or at least to provide the public with a useful choice.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF INVENTION

According to one aspect of the present invention there is provided a process for administering to an animal at least three progressively increasing doses of one or more biologically active agents which are released over a predetermined period of time from a delivery means which is administered to an animal on a single occasion.

Preferably said one or more biologically active agents are selected from the list of antibiotics, anthelmintics, peptides, proteins, carbohydrates, DNA, RNA, hormones, neutraceuticals, vitamins, trace-elements, immunising agents or any combination thereof.

The biologically active agents may optionally comprise an adjuvant and/or a pharmaceutically acceptable carrier.

Preferably the progressively increasing doses comprise sequentially doubling doses of biologically active agent, or sequentially increasing doses such as 25, 50, 75, 100 or 4, 8, 32, 150 active units. The doses are chosen so as to elicit a desired response and are administered over a predetermined period of time from hours, days, weeks, and months or any combination thereof.

Preferably said one or more biologically active agents is an immunising agent and wherein said process comprises the administration to said animal of progressively increasing doses of one or more immunising agents which are released over a predetermined period of time from a delivery means which is administered to an

an episode of infection and the natural antibody response thereto.

The doses of the progressively increasing doses of antigen are chosen so as to elicit a favourable antibody response which includes the production of both high-affinity antibodies and antigen-specific memory lymphocytes.

Preferably, the progressively increasing doses of antigen are in the range of from 0.1 μg to 1000 μg.

Preferably, the predetermined period of time at which the one or more drugs are administered is selected from hours, days, weeks or months or any combination thereof.

The delivery means preferably comprises an immunising agent delivery composition which comprises means to enable progressively increasing doses of one or more immunising agents to be released over a predetermined period of time therefrom, when said delivery means is administered to an animal on a single occasion.

The present invention further provides an unloaded delivery means comprising an unloaded immunising agent delivery composition which comprises means to enable at least three progressively increasing doses of one or more immunising agents to be released over a predetermined period of time once said immunising agent is loaded into said immunising agent delivery composition and when said delivery means is administered to an animal on a single occasion.

Preferably, the delivery composition comprises means to enable the delivery of one dose of said one or more antigens within hours/days/weeks/months of its administration and means to enable the delivery of further progressively increasing doses of the same or different antigens hours/days/weeks or months later.

The progressively increasing doses of said one or more immunising agents are

WHAT WE CLAIM IS:

1. A process for administering to an animal at least three progressively increasing doses of one or more biologically active agents which are released over a predetermined period of time from a delivery means which is administered to an animal on a single occasion.

2. A process as claimed in claim 1 wherein said one or more biologically active agents are selected from the list of antibiotics, anthelmintics, peptides, proteins, carbohydrates, DNA, RNA, hormones, neutraceuticals, vitamins, trace-elements, immunising agents or any combination thereof.

3. A process as claimed in either claim 1 of claim 2 wherein said one or more biologically active agents comprise an adjuvant and/or a pharmaceutically acceptable carrier.

4. A process as claimed in any one of claims 1 to 3 wherein the progressively increasing doses comprise sequentially doubling doses of biologically active agents, or sequentially increasing doses such as 25, 50, 75, 100 or 4, 8, 32, 150 active units.

5. A process as claimed in any one of claims 1 to 4 wherein the predetermined period of time at which said one or more of biologically active agents are administered is selected from hours, days, weeks or months or any combination thereof.

6. A process as claimed in any one of claims 1 to 5 wherein said one or more biologically active agents is an immunising agent and wherein said process comprises the administration to said animal of progressively increasing doses of one or more immunising agents which are released over a predetermined

period of time from a delivery means which is administered to an animal on a single occasion.

7. A process as claimed in claim 6 wherein said one or more immunising agents comprise an antigen or combination of antigens.

8. A process as claimed in claim 6 or claim 7 wherein said one or more immunising agents comprise a vaccine or combination of vaccines.

9. A process as claimed in any one of claims 6 to 8 wherein said one or more immunising agents are selected from molecules that will induce protective immunity against a disease causing organism, or functional immunity or any combination thereof.

10. A process as claimed in any one of claims 6 to 9 wherein the progressively increasing doses of said one or more immunising agents are in the range of from 0.1 μg to 1000 μg.

11. A process as claimed in any one of claims 6 to 10 wherein the delivery means comprises an immunising agent delivery composition which comprises means to enable progressively increasing doses of one or more immunising agents to be released over a predetermined period of time therefrom, when said delivery means is administered to an animal on a single occasion.

12. A biologically active agent delivery composition comprising one or more biologically active agents whereby said composition comprises means to enable at least three progressively increasing doses of said one or more biologically active agents to be released over a predetermined period of time from a delivery means which is administered to an animal on a single occasion.

13. A biologically active agent delivery composition as claimed in claim 12

25. A biologically active agent delivery composition as claimed in claim 24 wherein the administration of the delivery composition takes place shortly after birth of an animal, or when maternally-derived antibody has decreased sufficiently for the young animal to be able to respond to the vaccination, and provides immunity without the need for further booster administration.

26. A delivery means for use in a process as described in any one of claims 1 to 11 wherein the delivery composition is located within comprising a multi-compartmental capsule containing progressively increasing doses of one or more biologically active agents within the compartments, said delivery means comprising an outer wall made of a biodegradable substance which degrades over a pre-set period of time to release the smallest dose of biologically active agents, and one or more inner compartmental walls made of the same or different material that degrade over a longer period of time to release progressively increasing pulses of the biologically active agents

27. A delivery means as claimed in claim 26 wherein the biodegradable material of the outer wall is be selected from the group comprising cholesterol/lecithin, polylactide and/or polyglycolide copolymers, one or more of a number of cellulose polymers, polyacrylic acid, polymethylmethacrylate, cross-linked polyacrylic acid, polycaprolactone, polyvinylpyrrolidine, polyvinylalcohol, polyethylene glycol, agarose, DEAE dextran microspheres, starch microspheres and/or albumin microspheres or gelatine microspheres or any combination thereof.

28. A delivery means as claimed in claim 26 or claim 27 wherein the pre-set period of time within which the outer wall and inner compartmental walls degrade may be selected from hours, days, weeks or months.

29. A process substantially as described herein with reference to and as illustrated

by the accompanying description and drawings.

30. A biologically active agent delivery composition substantially as described herein with reference to and as illustrated by the accompanying description and drawings.